Dawn of a new therapeutic era for spinal muscular atrophy

Dawn of a new therapeutic era for SMA

The original papers reporting defects in the survival motor neuron (*SMN1*) gene as the underlying cause of spinal muscular atrophy (SMA) were published more than twenty years ago [1]. At the time, the identification of SMA as an essentially mono-genetic disorder was heralded as a major research breakthrough that would lead to the rapid development of new therapies. And yet, despite over two decades of intensive basic and pre-clinical research, no approved treatment options are currently available. Against this background, the new open-label, phase 2 clinical study by Finkel and colleagues published in this issue of The Lancet [2] represents a major milestone on the journey towards a viable therapy.

Mutations in the *SMN1* gene render it incapable of generating full-length survival motor neuron (SMN) protein [3]. The continuing presence of low levels of SMN protein in SMA patients results from the presence of a near-identical *SMN2* gene, the copy-number of which influences disease severity [4]. This 'backup' *SMN2* gene has a C→T substitution at an exon splice enhancer site that regulates exon 7 inclusion. As a result, only < 25% of *SMN2* transcripts contain exon 7 and are capable of producing full-length SMN protein. However, the retained presence of an *SMN2* gene in patients offers an opportunity for the development of therapies aimed at increasing levels of functional SMN protein, a strategy found to have remarkable potential in pre-clinical animal studies [5-6].

The Phase 2 clinical study by Finkel and colleagues [2] reports on the delivery of nusinersen, a 2'-O-methoxyethyl phosphorothioate-modified antisense drug designed to alter splicing of *SMN2* pre-mRNA and subsequently increase levels of SMN protein. Although data from a

Phase 1 trial of nusinersen in patients with less severe forms of SMA have already been published [7], the current study represents the first robust demonstration of safety and tolerability, as well as a positive pharmacokinetic profile, for nusinersen following multiple intrathecal doses in infants with the most severe form of SMA (Type I). Most importantly, the study confirmed successful uptake into motor neurons throughout the spinal cord, as well as other neuronal populations throughout the nervous system, leading to increased *SMN2* mRNA exon 7 inclusion and SMN protein levels. This establishes a critical proof-of-principle that it is possible to successfully target *SMN2* in order to elevate SMN protein levels across a range of affected cell types in SMA patients, without any major adverse consequences.

Finkel and colleagues [2] also present preliminary evidence suggesting that nusinersen can deliver incremental improvements in motor function for patients with severe forms of SMA. Whilst these findings need to be interpreted cautiously in the context of the obvious limitations of a small, open-label interventional trial, they should generate significant encouragement that elevating SMN protein levels is likely to be of therapeutic benefit to SMA patients.

Robust conclusions can not yet be drawn concerning the potential ability of nusinersen to influence broader aspects of the SMA phenotype, such as a requirement for permanent ventilation or age of death. This is largely due to the relatively small number of patients enrolled in the study and the need to draw quantitative comparisons with an unrelated, natural history case series. Indeed, it should be noted that promising clinical responses were not uniformly observed across all infants enrolled on the study. However, the overall direction of travel is clearly encouraging, with ongoing/future studies (including Phase 3 trials) likely to generate the additional clinical data required to gain a full appreciation of the potential therapeutic benefits of nusinersen treatment.

As predicted from pre-clinical animal studies, the Finkel et al [2] study indicates that restoration of SMN protein can modify disease severity, but does not represent a complete cure. Thus, ongoing efforts to develop a second generation of SMA therapies are likely to be key for developing fully effective treatments for SMA, applicable to patients with all sub-types of the condition. These include efforts to restore SMN protein earlier in disease progression (during a critical therapeutic/developmental time-window [8]), to facilitate systemic delivery of therapies throughout a range of additional peripheral tissues and organs [9-10], and to target additional SMN-independent pathways [11-12]. However, the promise of nusinersen demonstrated by Finkel and colleagues [2] represents a major first step forward, indeed a new dawn, in developing safe and effective therapy options for SMA that are urgently required.

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CONFLICT OF INTEREST STATEMENT

I am Chair of the Scientific Advisory Board of the SMA Trust and serve on scientific and clinical advisory boards for SMA Europe and AFM. I am named on a patent application

submitted by the University of Edinburgh for the use of beta-catenin inhibitors for the treatment of SMA.

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